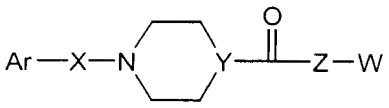
Claims

1. A compound according to the formula



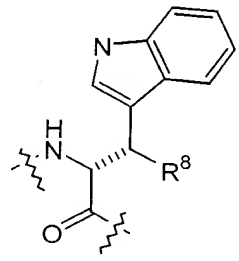
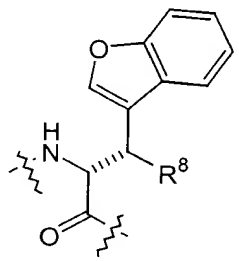
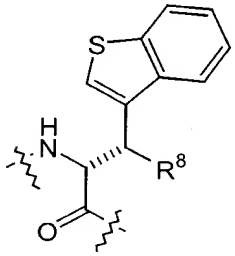
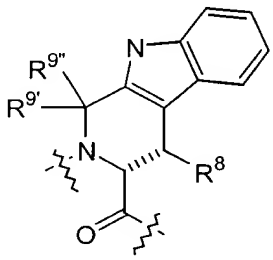
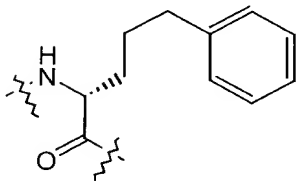
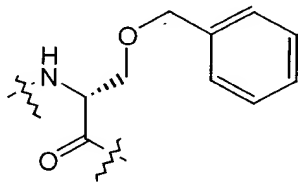
or a pharmaceutically acceptable salt, solvate or hydrate thereof; wherein

Ar is a (C_6-C_{10})aryl or (C_1-C_9)heteroaryl group that is optionally substituted;

X is a direct link, -CH_2 -, -SO_2 -, -CO-, -CHR^1- where R^1 is(C_1-C_6)alkyl, or -$CR^{1'}R^{1''}$- where both $R^{1'}$ and $R^{1''}$ are, independently, (C_1-C_6)alkyl;

Y is N or CH;

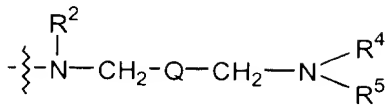
Z is selected from the groups consisting of:

wherein R^8, if present, is H, or (C_1-C_6) alkyl;

$R^{9'}$ and $R^{9''}$, if present, are each independently selected from the group consisting of H, (C_1-C_6)alkyl, (C_1-C_9)heteroaryl(C_1-C_6)alkyl, and (C_6-C_{10})aryl(C_1-C_6)alkyl;

W is selected from (a) and (b):

(a) 

wherein R^2, R^4 and R^5 are each independently selected from: H; $(C_1$-$C_6)$ alkyl, optionally substituted with one or more halo or trifluoromethyl groups; and benzyl, optionally substituted with one or more halo or trifluoromethyl groups; and

Q is selected from

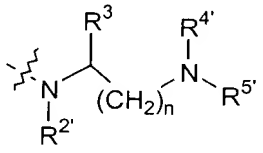
(i) $(C_6$-$C_{10})$ aryl;

(ii) $(C_1$-$C_9)$ heteroaryl;

(iii) $(C_3$-$C_{10})$cycloalkyl; and

(iv) $(C_3$-$C_{10})$heterocycloalkyl;

wherein each of said groups (i) to (iv) is optionally substituted with one or more groups that are independently selected from halo, $(C_1$-$C_6)$ alkoxy, and $(C_1$-$C_6)$ alkyl; and

(b) 

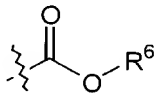
wherein

$R^{2'}$, $R^{4'}$ and $R^{5'}$ are each independently selected from the group consisting of H; $(C_1$-$C_6)$ alkyl, optionally substituted by one or more halo or trifluoromethyl groups; and benzyl, also optionally substituted by one or more halo or trifluoromethyl groups;

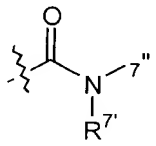
n is 2 to 5; and

R^3 is selected from the groups consisting of

(i) H; $(C_1$-$C_6)$alkyl, optionally substituted by one or more halo or trifluoromethyl groups; and benzyl, also optionally substituted by one or more halon or trifluoromethyl groups;

(ii) 

where R^6 is H; $(C_1$-$C_6)$alkyl, optionally substituted by one or more halo or trifluoromethyl groups; or benzyl, optionally substituted by one or more halo or trifluoromethyl groups; and

(iii) 

where $R^{7'}$ and $R^{7''}$ are each, independently, H; $(C_1\text{-}C_6)$alkyl, optionally substituted by one or more halo or trifluoromethyl groups; or benzyl, optionally substituted by one or more halo or trifluoromethyl groups.

2. The compound of claim 1, wherein group Ar is a $(C_6\text{-}C_{10})$ aryl group selected from phenyl and naphthyl.

3. The compound of claim 1, wherein group Ar is a a $(C_1\text{-}C_9)$ heteroaryl group that is selected from the group consisting of furyl, thienyl, thiazolyl, pyrazolyl, isothiazolyl, oxazolyl, isoxazolyl, pyrrolyl, triazolyl, tetrazolyl, imidazolyl, 1,3,5-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,3-oxadiazolyl, 1,3,5-thiadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, 1,3,5-triazinyl, pyrazolo[3,4-b]pyridinyl, cinnolinyl, pteridinyl, purinyl, 6,7-dihydro-5H-[1]pyrindinyl, benzo[b]thiophenyl, 5, 6, 7, 8-tetrahydro-quinolin-3-yl, benzoxazolyl, benzothiazolyl, benzisothiazolyl, benzisoxazolyl, benzimidazolyl, thianaphthenyl, isothianaphthenyl, benzofuranyl, isobenzofuranyl, isoindolyl, indolyl, indolizinyl, indazolyl, isoquinolyl, quinolyl, phthalazinyl, quinoxalinyl, quinazolinyl, and benzoxazinyl.

4. The compound of claim 1, wherein group Ar is optionally substituted by one to five groups, each independently selected from the group consisting of hydroxy, halo, amino, trifluoromethyl, carboxy, $(C_1\text{-}C_6)$alkoxy-, $(C_1\text{-}C_6)$acyloxy-, $(C_1\text{-}C_6)$alkylamino-, $((C_1\text{-}C_6)\text{alkyl})_2$amino-, $(C_1\text{-}C_6)$acylamino-, cyano, nitro, $(C_1\text{-}C_6)$alkyl-, $(C_2\text{-}C_6)$alkenyl-, $(C_2\text{-}C_6)$alkynyl-, $(C_1\text{-}C_6)$acylamino-, cyano$(C_1\text{-}C_6)$alkyl-, trifluoromethyl$(C_1\text{-}C_6)$alkyl-, nitro$(C_1\text{-}C_6)$alkyl-, $(C_1\text{-}C_3)$alkyl(difluoromethylene)$(C_1\text{-}C_3)$alkyl-, $(C_1\text{-}C_6)$acylamino$(C_1\text{-}C_6)$alkyl-, $(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_6)$acylamino-, amino$(C_1\text{-}C_6)$acyl-, amino$(C_1\text{-}C_6)$acyl$(C_1\text{-}C_6)$alkyl-, $(C_1\text{-}C_6)$alkylamino$(C_1\text{-}C_6)$acyl-, $((C_1\text{-}C_6)\text{alkyl})_2$amino$(C_1\text{-}C_6)$acyl-, $(C_3\text{-}C_{10})$cycloalkyl$(C_1\text{-}C_6)$alkyl-, $(C_1\text{-}C_6)$acyloxy$(C_1\text{-}C_6)$alkyl-, $(C_2\text{-}C_6)$alkoxy$(C_1\text{-}C_6)$alkyl-, piperazinyl$(C_1\text{-}C_6)$alkyl-, $(C_1\text{-}C_6)$acylamino$(C_1\text{-}C_6)$alkyl-, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_6)$alkyl-, $(C_2\text{-}C_9)$heteroaryl$(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_6)$alkyl-, $(C_1\text{-}C_6)$alkylthio$(C_1\text{-}C_6)$alkyl-, $(C_6\text{-}C_{10})$arylthio$(C_1\text{-}C_6)$alkyl-, $(C_1\text{-}C_6)$alkylsulfinyl$(C_1\text{-}C_6)$alkyl- $(C_6\text{-}C_{10})$arylsulfinyl$(C_1\text{-}C_6)$alkyl-, $(C_1\text{-}C_6)$alkylsulfonyl$(C_1\text{-}C_6)$alkyl-, $(C_6\text{-}C_{10})$arylsulfonyl$(C_1\text{-}C_6)$alkyl-, amino$(C_1\text{-}C_6)$alkyl-, $(C_1\text{-}C_6)$alkylamino$(C_1\text{-}C_6)$alkyl-, $(C_1\text{-}C_6)$alkyl(difluoromethylene)-, $(C_1\text{-}C_3)$alkyl(difluoromethylene)$(C_1\text{-}C_3)$alkyl-, $(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_6)$acyl-, $(C_1\text{-}C_6)$alkylamino$(C_1\text{-}C_6)$acyl-, $((C_1\text{-}C_6)\text{alkyl})_2$amino$(C_1\text{-}C_6)$acyl-, $(C_6\text{-}C_{10})$aryl-, $(C_5\text{-}C_9)$heteroaryl-, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl-, $(C_2\text{-}C_9)$heteroaryl$(C_1\text{-}C_6)$alkyl-, $(C_6\text{-}C_{10})$aryl$(C_6\text{-}C_{10})$aryl-, $(C_6\text{-}C_{10})$aryl$(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl- $(C_3\text{-}C_{10})$cycloalkyl-, $(C_3\text{-}C_6)$cycloalkyl$(C_1\text{-}C_6)$alkyl-, $(C_3\text{-}C_{10})$heterocycloalkyl-, $(C_3\text{-}C_{10})$heterocycloalkyl$(C_1\text{-}C_6)$alkyl-, hydroxy$(C_2\text{-}C_6)$alkyl-, $(C_1\text{-}$

C_6)acyloxy(C_2-C_6)alkyl-, (C_1-C_6)alkoxy(C_2-C_6)alkyl-, piperazinyl(C_1-C_6)alkyl-, (C_1-C_6)acylamino(C_1-C_6)alkyl-, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C_1-C_6)alkyl-, (C_2-C_9)heteroaryl(C_1-C_6)alkoxy(C_1-C_6)alkyl-, (C_1-C_6)alkylthio(C_1-C_6)alkyl-, (C_6-C_{10})arylthio(C_1-C_6)alkyl-, (C_1-C_6)alkylsulfinyl(C_1-C_6)alkyl-, (C_6-C_{10})arylsulfinyl(C_1-C_6)alkyl-, (C_1-C_6)alkylsulfonyl(C_1-C_6)alkyl-, (C_6-C_{10})arylsulfonyl(C_1-C_6)alkyl-, amino(C_1-C_6)alkyl-, (C_1-C_6)alkylamino(C_1-C_6)alkyl-, and ((C_1-C_6)alkyl)$_2$amino(C_1-C_6)alkyl.

5. The compound of claim 1, wherein group Q of group W, option (a), is a (C_6-C_{10}) aryl group selected from phenyl and naphthyl.

6. The compound of claim 1, wherein group Q of group W, option (a), is a (C_1-C_9) heteroaryl group that is selected from the group consisting of furyl, thienyl, thiazolyl, pyrazolyl, isothiazolyl, oxazolyl, isoxazolyl, pyrrolyl, triazolyl, tetrazolyl, imidazolyl, 1,3,5-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,3-oxadiazolyl, 1,3,5-thiadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, 1,3,5-triazinyl, pyrazolo[3,4-b]pyridinyl, cinnolinyl, pteridinyl, purinyl, 6,7-dihydro-5H-[1]pyrindinyl, benzo[b]thiophenyl, 5, 6, 7, 8-tetrahydro-quinolin-3-yl, benzoxazolyl, benzothiazolyl, benzisothiazolyl, benzisoxazolyl, benzimidazolyl, thianaphthenyl, isothianaphthenyl, benzofuranyl, isobenzofuranyl, isoindolyl, indolyl, indolizinyl, indazolyl, isoquinolyl, quinolyl, phthalazinyl, quinoxalinyl, quinazolinyl, and benzoxazinyl.

7. The compound of claim 1, wherein group Q of group W, option (a), is a (C_3-C_{10})cycloalkyl group that is selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, 1,3-cyclobutadienyl, 1,3-cyclopentadienyl, 1,3-cyclohexadienyl, 1,4-cyclohexadienyl, 1,3-cycloheptadienyl, 1,4-cycloheptadienyl, 1,3,5-cycloheptatrienyl, bicyclo[3.2.1]octane, bicyclo [2.2.1] heptane, and the norborn-2-ene unsaturated form thereof.

8. The compound of claim 1, wherein group Q of group W, option (a), is a (C_3-C_{10})heterocycloalkyl group that is selected from the group consisting of pyrrolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydropyranyl, pyranyl, thiopyranyl, aziridinyl, oxiranyl, methylenedioxyl, chromenyl, isoxazolidinyl, 1,3-oxazolidin-3-yl, isothiazolidinyl, 1,3-thiazolidin-3-yl, 1,2-pyrazolidin-2-yl, 1,3-pyrazolidin-1-yl, piperidinyl, thiomorpholinyl, 1,2-tetrahydrothiazin-2-yl, 1,3-tetrahydrothiazin-3-yl, tetrahydrothiadiazinyl, morpholinyl, 1,2-tetrahydrodiazin-2-yl, 1,3-tetrahydrodiazin-1-yl, tetrahydroazepinyl, piperazinyl, and chromanyl.

9. The compound of claim 1, selected from the group consisting of:

6-Amino-2-[2-[(1-benzenesulfonyl-piperidine-4-carbonyl)-amino]-3-(1H-indol-3-yl)-propionylamino]-hexanoic acid tert-butyl ester;

6-Amino-2-[2-[(4-benzoyl-piperazine-1-carbonyl)-amino]-3-(1H-indol-3-yl)-propionylamino]-hexanoic acid tert-butyl ester;

6-Amino-2-(3-(1H-indol-3-yl)-2-{[4-(4-methyl-benzoyl)-piperazine-1-carbonyl]-amino}-propionylamino)-hexanoic acid tert-butyl ester;

6-Amino-2-[2-[(4-benzenesulfonyl-piperazine-1-carbonyl)-amino]-3-(1H-indol-3-yl)-propionylamino]-hexanoic acid tert-butyl ester; and

6-Amino-2-(3-(1H-indol-3-yl)-2-{[4-(toluene-4-sulfonyl)-piperazine-1-carbonyl]-amino}-propionylamino)-hexanoic acid tert-butyl ester.

10. The compound of claim 1, selected from the group consisting of:

4-(Toluene-4-sulfonyl)-piperazine-1-carboxylic acid [1-[(4-aminomethyl-pyridin-2-ylmethyl)-carbamoyl]-2-(1H-indol-3-yl)-ethyl]-amide;

6-Amino-2-(3-(1H-indol-3-yl)-2-{[4-(toluene-4-sulfonyl)-piperazine-1-carbonyl]-amino}-butyrylamino)-hexanoic acid tert-butyl ester;

6-Amino-2-[2-{[4-(4-fluoro-benzenesulfonyl)-piperazine-1-carbonyl]-amino}-3-(1H-indol-3-yl)-propionylamino]-hexanoic acid tert-butyl ester;

4-Benzenesulfonyl-piperazine-1-carboxylic acid [1-[(4-aminomethyl-pyridin-2-ylmethyl)-carbamoyl]-2-(1H-indol-3-yl)-ethyl]-amide;

6-Amino-2-[2-[(4-benzenesulfonyl-piperazine-1-carbonyl)-amino]-3-(1H-indol-3-yl)-butyrylamino]-hexanoic acid tert-butyl ester;

6-Amino-2-[2-{[4-(4-chloro-benzenesulfonyl)-piperazine-1-carbonyl]-amino}-3-(1H-indol-3-yl)-propionylamino]-hexanoic acid tert-butyl ester;

4-(4-Methyl-benzoyl)-piperazine-1-carboxylic acid [1-[(4-aminomethyl-pyridin-2-ylmethyl)-carbamoyl]-2-(1H-indol-3-yl)-ethyl]-amide;

6-Amino-2-(3-(1H-indol-3-yl)-2-{[4-(4-methyl-benzoyl)-piperazine-1-carbonyl]-amino}-butyrylamino)-hexanoic acid tert-butyl ester;

6-Amino-2-[2-{[4-(4-fluoro-benzoyl)-piperazine-1-carbonyl]-amino}-3-(1H-indol-3-yl)-propionylamino]-hexanoic acid tert-butyl ester;

4-Benzoyl-piperazine-1-carboxylic acid [1-[(4-aminomethyl-pyridin-2-ylmethyl)-carbamoyl]-2-(1H-indol-3-yl)-ethyl]-amide;

6-Amino-2-[2-[(4-benzoyl-piperazine-1-carbonyl)-amino]-3-(1H-indol-3-yl)-butyrylamino]-hexanoic acid tert-butyl ester;

6-Amino-2-[2-{[4-(4-chloro-benzoyl)-piperazine-1-carbonyl]-amino}-3-(1H-indol-3-yl)-propionylamino]-hexanoic acid tert-butyl ester;

1-(Toluene-4-sulfonyl)-piperidine-4-carboxylic acid [1-[(4-aminomethyl-pyridin-2-ylmethyl)-carbamoyl]-2-(1H-indol-3-yl)-ethyl]-amide;

6-Amino-2-(3-(1H-indol-3-yl)-2-{[1-(toluene-4-sulfonyl)-piperidine-4-carbonyl]-amino}-butyrylamino)-hexanoic acid tert-butyl ester;

6-Amino-2-[2-{[1-(4-fluoro-benzenesulfonyl)-piperidine-4-carbonyl]-amino}-3-(1H-indol-3-yl)-propionylamino]-hexanoic acid tert-butyl ester;

1-Benzenesulfonyl-piperidine-4-carboxylic acid [1-[(4-aminomethyl-pyridin-2-ylmethyl)-carbamoyl]-2-(1H-indol-3-yl)-ethyl]-amide;

6-Amino-2-[2-[(1-benzenesulfonyl-piperidine-4-carbonyl)-amino]-3-(1H-indol-3-yl)-butyrylamino]-hexanoic acid tert-butyl ester;

6-Amino-2-[2-{[1-(4-chloro-benzenesulfonyl)-piperidine-4-carbonyl]-amino}-3-(1H-indol-3-yl)-propionylamino]-hexanoic acid tert-butyl ester;

1-(4-Methyl-benzoyl)-piperidine-4-carboxylic acid [1-[(4-aminomethyl-pyridin-2-ylmethyl)-carbamoyl]-2-(1H-indol-3-yl)-ethyl]-amide;

6-Amino-2-(3-(1H-indol-3-yl)-2-{[1-(4-methyl-benzoyl)-piperidine-4-carbonyl]-amino}-butyrylamino)-hexanoic acid tert-butyl ester;

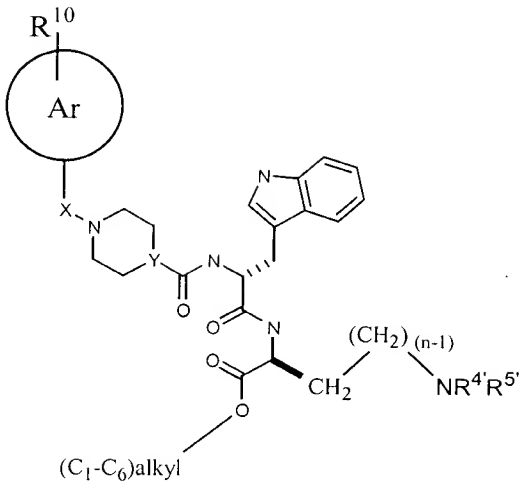
6-Amino-2-[2-{[1-(4-fluoro-benzoyl)-piperidine-4-carbonyl]-amino}-3-(1H-indol-3-yl)-propionylamino]-hexanoic acid tert-butyl ester;

1-Benzoyl-piperidine-4-carboxylic acid [1-[(4-aminomethyl-pyridin-2-ylmethyl)-carbamoyl]-2-(1H-indol-3-yl)-ethyl]-amide;

6-Amino-2-[2-[(1-benzoyl-piperidine-4-carbonyl)-amino]-3-(1H-indol-3-yl)-butyrylamino]-hexanoic acid tert-butyl ester; and

6-Amino-2-[2-{[1-(4-chloro-benzoyl)-piperidine-4-carbonyl]-amino}-3-(1H-indol-3-yl)-propionylamino]-hexanoic acid tert-butyl ester.

11. A compound according to the formula



or a pharmaceutically acceptable salt, solvate, or hydrate thereof; wherein

Ar is a $(C_6\text{-}C_{10})$aryl or $(C_1\text{-}C_9)$heteroaryl group that is optionally substituted;

X is a direct link, $-CH_2-$, $-SO_2-$, -CO-, $-CHR^1-$ where R^1 is $(C_1\text{-}C_6)$alkyl, or $-CR^{1'}R^{1''}-$ where both $R^{1'}$ and $R^{1''}$ are, independently, $(C_1\text{-}C_6)$alkyl;

Y is N or CH;

R^{10} represents from 0 to 5 optional substituent groups, each independently selected from halo, cyano, carboxy, $(C_1\text{-}C_6)$alkyl, and $(C_1\text{-}C_6)$alkoxy;

$R^{4'}$ and $R^{5'}$ are each independently selected from H; $(C_1\text{-}C_8)$ alkyl, optionally substituted by one or more halo or trifluoromethyl groups; and benzyl, also optionally substituted by one or more halo or trifluoromethyl groups; and

n is 1 to 4.

12. A compound according to claim 1 wherein R^2 or $R^{2'}$ is $(C_1\text{-}C_8)$alkyl- or benzyl-, optionally substituted by one or more halo or trifluoromethyl groups.

13. A compound according to claim 1 wherein one or more of R^3, R^4, $R^{4'}$, R^5, $R^{5'}$, and R^6 is $(C_1\text{-}C_8)$alkyl- or benzyl-, optionally substituted by one or more halo or trifluoromethyl groups.

14. A compound according to claim 1 wherein R^7 or $R^{7'}$ is $(C_1\text{-}C_8)$alkyl- or benzyl-, optionally substituted by one or more halo or trifluoromethyl groups.

15. A pharmaceutical composition for increasing growth hormone secretion in a mammal, comprising an effective amount of a compound according to claim 1, and a pharmaceutical carrier.

16. A pharmaceutical composition for increasing secretion of gastrin or glucagon in a mammal, comprising an effective amount of a compound according to claim 1, and a pharmaceutical carrier.

17. A pharmaceutical composition for inhibiting the binding of somatostatin to an sst2 receptor, comprising an effective amount of a compound according to claim 1, and a pharmaceutical carrier.

18. A method for increasing growth hormone secretion in a mammal, comprising administering an effective amount of a pharmaceutical composition according to claim 15.

19. A method for increasing secretion of gastrin or glucagon in a mammal, comprising administering an effective amount of a pharmaceutical composition according to claim 16.

20. A method for decreasing somatostatin-induced downregulation of growth hormone secretion in a mammal, comprising administering an effective amount of a pharmaceutical composition according to claim 17.

21. A pharmaceutical composition useful to cause sustained release of growth hormone in a mammal in need thereof, comprising a compound according to claim 1, and a pharmaceutical carrier.

22. A method for facilitating the sustained secretion of growth hormone in a mammal in need thereof, wherein said mammal possesses:

(a) a defect in (1) the expression of the encoding nucleotide sequence for growth hormone, (2) the processing of resultant mRNA, or (3) the translation or intracellular processing and packaging of GH or precursor polypeptide thereof; or

(b) an allele of the growth hormone gene which codes for a growth hormone polypeptide that is insufficiently active;

which comprises administering an effective amount of a pharmaceutical composition according to claim 21.

23. A method for treating a human for one or more symptoms of insufficient growth hormone secretion, wherein said symptom is selected from frailty, hypoglycemia,

wrinkled skin, slow skeletal growth, reduced immune function, and reduced organ function, comprising administering an effective amount of a pharmaceutical composition according to claim 15.

24. A method for treating a non-human mammal to enhance the growth and performance thereof, comprising administering an effective amount of a pharmaceutical composition according to claim 15.

25. A pharmaceutical composition according to claim 15 further comprising growth hormone releasing peptide (GHRP) or growth hormone releasing hormone (GHRH).

26. A method for increasing growth hormone secretion in a mammal, comprising administering an effective amount of a pharmaceutical composition according to claim 25.

27. A method for increasing growth hormone secretion in a mammal, comprising administering an effective amount of a pharmaceutical composition according to claim 15, and a further composition comprising growth hormone releasing peptide (GHRP) or growth hormone releasing hormone (GHRH).